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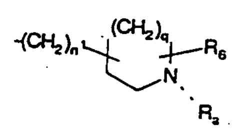
(54) Title: BENZOPYRAN, BENZOTHIOPYRAN AND BENZOFURAN DERIVATIVES AS 5-HT4 ANTAGONISTS



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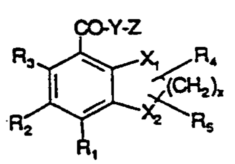
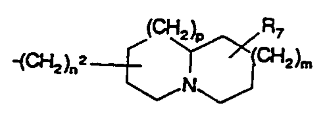


(I)



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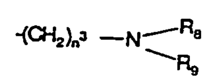


(c)

(57) Abstract

Compounds of formula (I) and pharmaceutically acceptable salts thereof, in which X_1-$(CH_2)_x$-X_2 and the aromatic carbon atoms to which they are attached form a 5-7 membered ring wherein: one of X_1 and X_2 is O, S or CH_2 and the other is CH_2; x is 1, 2 or 3; R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy; R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio; R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino; R_4 and R_5 are independently hydrogen or C_{1-6} alkyl; Y is O or NH; Z is of sub-formula (a), (b) or (c), wherein n^1 is 1, 2, 3 or 4; n^2 is 1 or 2; n^3 is 2, 3, 4 or 5; q is 0, 1, 2 or 3; p is 0, 1 or 2; m is 0, 1 or 2; R_a is hydrogen or a lipophilic group, such as C_{1-12} alkyl or aralkyl; or R_a is $(CH_2)_r$-R_{10} wherein r is 2 or 3 and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, $-CR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl; and R_6, R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and R_9 is hydrogen or C_{1-10} alkyl; or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere; and their use as pharmaceuticals in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

Benzopyran, benzothiopyran and benzofuran derivatives as 5-HT4 antagonists

This invention relates to the use of compounds as 5-HT_4 receptor antagonists in the treatment of gastrointestinal disorders, CNS disorders including migraine and/or cardiovascular disorders, and to certain novel compounds having 5-HT_4 receptor antagonist activity.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that ICS 205-930, which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor.

WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT_4 antagonist activity.

Some 5-HT_3 receptor antagonists have been disclosed as of potential use in the treatment of certain aspects of irritable bowel syndrome [EP-A-189002 (Sandoz Limited) and EP-A-201165 (Beecham Group p.l.c)].

5-HT_3 receptor interactions which are of potential use in the treatment of IBS are those associated either with the visceral pain and abnormal perception of sensation aspects of this disease, or they are related to the ability of some 5-HT_3 receptor antagonists to cause constipation in volunteers.

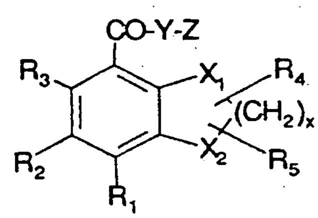
Some 5-HT_3 receptor antagonists have been disclosed as of potential use in the treatment of gastrointestinal disorders associated with upper gut motility [EP-A-226266 (Glaxo Group Ltd.) and EP-A-189002 (Sandoz Limited)]. 5-HT_3 receptor antagonists are also well known antiemetics, such as ondansetron, granisetron and tropisetron [Drugs of the Future 1989, 14 (9) p.875 - F.D. King and G.J. Sanger].

EP-A-234872 (Adria), US 4859683 (Rorer) and EP-A-307172 (Lilly) describe 5-HT_3 receptor antagonists derived from a benzoic acid nucleus, 2,3-disubstituted by alkyleneoxy.

It has now been discovered that certain of the compounds embraced by the general formulae disclosed therein, and related compounds, have 5-HT_4 receptor antagonist properties, and are therefore of potential use in the treatment of IBS or atrial arrhythmias and stroke.

The compounds of the present invention also have a potential use in the treatment of CNS disorders such as anxiety and/or migraine, in the treatment of upper gut motility disorders and as antiemetics.

Accordingly, the present invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

in which X_1-$(CH_2)_x$-X_2 and the aromatic carbon atoms to which they are attached form a 5-7 membered ring

wherein:

one of X_1 and X_2 is O, S or CH_2 and the other is CH_2;

x is 1, 2 or 3;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

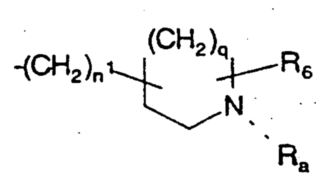
R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

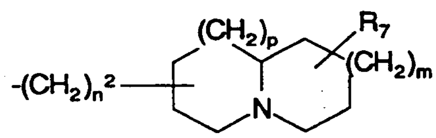
R_4 and R_5 are independently hydrogen or C_{1-6} alkyl;

Y is O or NH;

Z is of sub-formula (a), (b) or (c):



(a)



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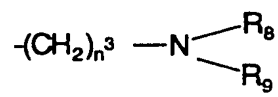


(c)

wherein

n^1 is 1, 2, 3 or 4; n^2 is 1 or 2; n^3 is 2, 3, 4 or 5;

q is 0, 1, 2 or 3; p is 0, 1 or 2; m is 0, 1 or 2;

R_a is hydrogen or a lipophilic group, such as C_{1-12} alkyl or aralkyl; or

R_a is $(CH_2)_r$-R_{10} wherein r is 2 or 3 and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, $-CR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl; and

R_6, R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and

R_9 is hydrogen or C_{1-10} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

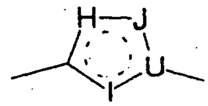
in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

Examples of alkyl or alkyl containing groups include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} or C_{12} branched, straight chained or cyclic alkyl, as appropriate. C_{1-4} alkyl groups include methyl, ethyl *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Cyclic alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Aryl includes phenyl and naphthyl optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy.

Halo includes fluoro, chloro, bromo and iodo,.

A suitable bioisostere for the amide or ester linkage containing Y in formula (I), is of formula (d)



(d)

wherein
the dotted circle represents one or two double bonds in any position in the 5-membered ring; H, J and I independently represent oxygen, sulphur, nitrogen or carbon, provided that at least one of H, J and I is other than carbon; U represents nitrogen or carbon.

Suitable examples of (d) are as described for X, Y and Z in EP-A-328200 (Merck Sharp & Dohme Ltd.), such as an oxadiazole moiety.

Suitable examples of the X_1-$(CH_2)_x$-X_2 include O-$(CH_2)_2$-CH_2, O-$(CH_2)_3$-CH_2, O-CH_2-CH_2, or corresponding values wherein $X_1 = X_2 = CH_2$, wherein any of the methylene linkages are optionally mono- or di-substituted by C_{1-6} alkyl groups, such as methyl. Preferably X_1-$(CH_2)_2$-X_2 is O-$(CH_2)_2$-CH_2.

R_1 is preferably hydrogen or amino.

R_2 is preferably hydrogen or halo.

R_3 is preferably hydrogen or halo.

R_4 and R_5 are often hydrogen. When R_4/R_5 is C_{1-6} alkyl, it is often methyl. In particular R_4 and R_5 are methyl such that the disubstituent containing X_1 and X_2 is X_1-$C(CH_3)_2$-X_2.

Y is preferably O or NH.

When Z is of sub-formula (a), n^1 is preferably 2, 3 or 4 when the azacycle is attached at the nitrogen atom and n^1 is preferably 1 when the azacycle is attached at a carbon atom, such as the 4-position when q is 2.

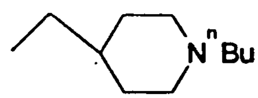
When Z is of sub-formula (b), n^2 is preferably such that the number of carbon atoms between the ester or amide linkage is from 2 to 4 carbon atoms.

Suitable values for p and m include p = m = 1; p = 0, m = 1; p = 1, m = 2.

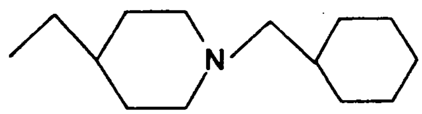
When Z is of sub-formula (c), n^3 is preferably 2, 3 or 4.

R_8 and R_9 are preferably both alkyl, especially one of R_8 and R_9 is C_4 or larger alkyl.

Specific values of Z of particular interest are as follows:



(i)



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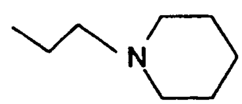

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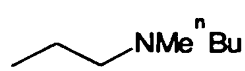

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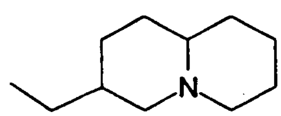
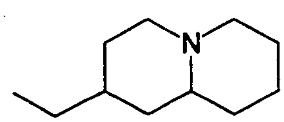


(v)



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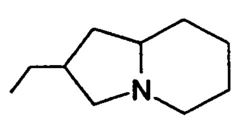


(vii)

The invention also provides novel compounds within formula (I) with side chains (i), (ii), (iii), (iv), (v), (vi) or (vii). In a further aspect, the piperidine ring in (i), (ii) or (iii) may be replaced by pyrrolidinyl or azetidinyl, and/or the N-substituent in (i) or (ii) may be replaced by C_3 or larger alkyl or optionally substituted benzyl.

In an alternative aspect, the N-substituent in formula (i) or (ii) may be replaced by $(CH_2)_nR^4$, as defined in formula(I) and in relation to the specific examples of EP-A-501322.

The invention also provides novel compounds within formula (I) having X_1-$(CH_2)_x$-X_2 as O-$(CH_2)_2$-CH_2, in particular those wherein the side chain Z is of sub-formula (a) or (c).

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

It will also be realised that the $(CH_2)_n2$ moiety in compounds of formula (I) wherein Z is (b), may adopt an α or β or configuration with respect to the fused azabicyclic moiety.

The compounds of formula (I) wherein CO-Y is an ester or amide linkage are prepared by conventional coupling of the Z moiety with the appropriate acid. Suitable methods are as described in GB 2125398A (Sandoz Limited), GB 1593146A, EP-A-36269 and EP-A-289170 (Beecham Group p.l.c.). When CO-Y is replaced by a heterocyclic bioisostere, suitable methods are described in EP-A-328200 (Merck Sharp & Dohme Limited). Reference is also made to EP-A-501322 (Glaxo Group Limited).

Aza(bi)cyclic side chain intermediates are known compounds or may be prepared according to the methods described in PCT/GB92/01519 and /01612 (SmithKline Beecham p.l.c.).

The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic agent induced emesis.

Specific cardiac 5-HT_4 receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

Anxiolytic activity is likely to be effected via the hippocampus (Dumais *et al* 1988, Mol Pharmacol., 34, 880-887). Activity can be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT_4 receptors, and hence that administration of a 5-HT_4 antagonist is of potential benefit in relieving a migraine attack.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl

cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of irritable bowel syndrome, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of irritable bowel syndrome, gastro-oesophageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine.

The following Examples illustrate the preparation of compounds of formula (I); the following descriptions relate to intermediates.

A preferred compound corresponds to any example, but wherein there is an amino substituent in the 4-position and a chloro substituent in the 5-position of the benzoic acid nucleus depicted in formula (I).

Examples

	R_1	R_2	R_3	X_1/X_2	Y	Z
E1	H	H	H	$O-(CH_2)_2-CH_2$	O	(i)
E2	H	H	H	$O-CH_2-CH_2$	O	(i)
E3	H	Cl	H	$O-(CH_2)_2-CH_2$	O	(i)
E4	H	H	H	$O-CH(CH_3)_2-(CH_2)_2$	O	(i)
E5	H	Cl	H	$O-CH(CH_3)_2-CH_2$	O	(i)
E6	NH_2	Cl	H	$O-(CH_2)_2-CH_2$	O	(i)
E7	H	Cl	H	$O-(CH_2)_2-CH_2$	O	(iii)
E8	H	Cl	H	$O-(CH_2)_2-CH_2$	NH	(i)
E9	H	Cl	H	$O-CH(CH_3)_2-(CH_2)_2$	O	(i)
E10	H	H	H	$S-(CH_2)_2-CH_2$	O	(i)
E11	H	Br	H	$S-(CH_2)_2-CH_2$	O	(i)
E12	NH_2	Cl	H	$O-(CH_2)_2-CH_2$	NH	(i)

Example 1

(1-Butyl-4-piperidyl)methyl-[2H]-3,4-dihydro-1-benzopyran-8-carboxylate (E1)

To a stirred solution of [2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid (0.3g) in dichloromethane (15ml) at 0^{o}C under nitrogen, was added oxalyl chloride (0.16 ml) and dry dimethylformamide (3m drops). After 1 hour, the solvents were evaporated under reduced pressure. The residual acid chloride was dissolved in dry THF (20 ml) and added dropwise to a solution of the lithium anion of 1-butyl-4-piperidinemethanol in dry THF, prepared by treating a solution of 1-butyl-4-piperidinemethanol (0.29g) in dry THF (20ml) with butyllithium (1.1ml of a 1.6 molar solution in hexane), at 0^{o}C under nitrogen for 15 minutes. After stirring at ambient temperature overnight, the reaction mixture was diluted with water, the volatile solvent was evaporated under reduced pressure, and the product was extracted into dichloromethane. The organic phase was dried (Na_2SO_4) and the solvent was evaporated under reduced pressure. The residue was chromatographed through a short flash silica column using an increasing proportion of methanol in chloroform (1%, 2%). The product was isolated as the hydrochloride salt from IPA/Et_2O to give the title compound (177mg).

mp 166-8^{o}C.

^{1}H NMR 250MHz ($CDCl_3$) (free base)

δ: 7.62(d,1H), 7.19(d,1H), 6.85(t,1H), 4.30(t,2H), 4.15(d,2H), 3.02(d,2H), 2.83(t,2H), 2.45-2.25(m,2H), 2.1-1.9(m,4H), 1.9-1.65(m,3H), 1.6-1.2(m,6H), 0.92(t,3H)

Example 2

(1-Butyl-4-piperidyl)methyl-2,3-dihydrobenzofuran-7-carboxylate hydrochloride (E2)

To a stirred solution of 2,3-dihydrobenzofuran-7-carboxylic acid (D1) (0.2g) in dichloromethane (15ml) at 0^{o}C under nitrogen was added oxalyl chloride (0.12ml) and dry dimethylformamide (3 drops). After 1 hour the solvents were evaporated under reduced pressure. The residual acid chloride was dissolved in dichloromethane (15ml) and treated with a solution of 1-butyl-4-piperidine methanol (0.21g) in dichloromethane (10ml) and triethylamine (0.19ml). After stirring at ambient temperature overnight, the reaction mixture was washed with saturated $NaHCO_3$ and the organic phase was dried (Na_2SO_4). The solvent was evaporated under reduced pressure and the residue chromatographed through a short flash silica column, eluting with increasing proportions of methanol in chloroform (1%, 2%). The product was isolated as the hydrochloride salt from IPA/Et_2O to give the title compound (84 mg).

mp 187-9^{o}C

^{1}H NMR 250MHz ($CDCl_3$) (free base)

δ: 7.72(d,1H), 7.35(d,1H), 6.88(t,1H), 4.72(t,2H), 4.19(d,2H), 3.22(t,2H), 3.1-2.9(d,2H), 2.5-2.25(m,2H), 2.1-1.2(m, 11H), 0.92(t,3H)

Example 3

(1-Butyl-4-piperidyl)methyl-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylate (E3)

Following the procedure outlined in Example 1 (except that methyllithium was used in a place of n-butyllithium), 6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid (300 mg) was converted to the title compound (143 mg, 28%).

^{1}H NMR 250 MHz ($CDCl_3$)

δ: 7.55 (s, 1H), 7.15 (s, 1H), 4.29 (t, 2H), 4.15 (d, 2H), 3.05 (brd, 2H), 2.80 (t, 2H), 2.5-2.25 (m, 2H), 2.18-1.10 (m, 13H), 0.94 (t, 3H)

Example 4

2,2-Dimethyl-[2H]-3,4-dihydro-1-benzopyran-8-(1-butyl-4-piperidyl)methylcarboxylate hydrochloride (E4)

To a solution of 2,2-dimethyl-[2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid (EP-A-307172) (300 mg) in acetonitrile (20 ml) was added N, N'-carbonyldiimidazole (236mg). Stirring was continued at ambient temperature for 1h. The solvent was concentrated *in vacuo* to afford crude imidazolide.

Methyllithium (1.5M in diethyl ether, 0.97 ml) was added dropwise to a cooled (0°C) solution of 1-butyl-4-piperidinemethanol (250 mg) in dry THF (10 ml) under a nitrogen atmosphere. Stirring was continued at room temperature for 10 min. A solution of the imidazolide in dry THF (10ml) was added and stirring continued overnight. Water was added and the solvent concentrated *in vacuo*. The residue was partitioned between chloroform and water. The organic phase was dried (Na_2SO_4), filtered and concentrated. The residue was chromatographed on silica using chloroform and ethanol as eluant to afford pure ester (471 mg) as an oil. Treatment with ethereal HCl and trituration of the resultant gum with diethyl ether gave title compound as a solid.

^{1}H NMR 250 MHz ($CDCl_3$)

δ: 7.60(d,1H), 7.19(d,1H), 6.82(t,1H), 3.99(d,2H), 2.93-3.03(m,2H), 2.81(t,2H), 2.28-2.37(m,2H), 1.61-2.02(m,7H), 1.23-1.56(m,12H inc s,6H), 0.94(t,3H)

Example 5

7-(1-Butyl-4-piperidyl)methyl-5-chloro-2,3-dihydro-2,2-dimethyl-benzofurancarboxylate (E5)

Following the procedure outlined in Example 4, 5-chloro-2,3-dihydro-2,2-dimethylbenzofuran-7-carboxylic acid was converted to the title compound.

mp 225-6°C (hydrochloride salt)

^{1}H NMR 250MHz ($CDCl_3$) (free base)

δ: 7.65(d,1H), 7.22 (d,1H), 4.12(d,2H), 2.92-3.11 (m,4H incl. s2H), 2.28-2.38 (m,2H), 1.22-2.0 (m, 17H inc s,6H), 0.92 (t,3H)

Example 6

(1-Butyl-4-piperidyl)methyl-5-amino-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylate hydrochloride (E6)

Following the procedure outlined in Example 4, 5-amino-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid (D4) (200mg) was converted to the title compound (68mg 19%).

mp 209-213°C

^{1}H NMR 250 MHz ($CDCl_3$) (free base)

δ: 7.7(s,1H), 4.39(brs, 2H), 4.22(t,2H), 4.10(d,2H), 3.05(brd,2H), 2.6-2.25(m,4H), 2.2-1.93(m,4H), 1.9-1.68(m,3H), 1.65-1.2(m,6H), 0.92(t,3H)

Example 7

(1-Piperidyl)ethyl-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylate hydrochloride (E7)

Following the procedure outlined in Example 1, except that MeLi was used in place of butyllithium, 6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid (390mg) was converted to the title compound (182mg, 28%) mp 185-7^oC.

^1H NMR 250 MHz ($CDCl_3$) (free base)

δ: 7.58(s,1H), 7.15(s,1H), 4.4(t,2H), 4.29(t,2H), 2.88-2.65(m,4H), 2.6-2.35(m,4H), 2.15-1.9(m,2H), 1.7-1.3(m,6H)

Example 8

(1-Butyl-4-piperidyl)methyl-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxamide hydrochloride (E8)

A solution of 6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid (200mg) in dry dichloromethane (6ml) was treated with oxalyl chloride (0.13 ml) and dry dimethylformamide (2 drops) under nitrogen. After stirring for four hours at ambient temperature the solvent was evaporated under reduced pressure. The resulting acid chloride was dissolved in dry dichloromethane (6ml) and added to a stirring solution of 1-butylpiperidin-4-ylmethylamine (160mg) in dry dichloromethane (5ml) containing triethylamine (0.14 ml). After stirring at ambient temperature overnight under nitrogen, the reaction mixture was washed with $NaHCO_3$ and the organic phase dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give the product which was purified using column chromatography (SiO_2, methanol/chloroform), and converted to the hydrochloride salt (E61) (138mg, 37%) mp 227-9^oC.

^{1}H NMR 250 MHz ($CDCl_3$) (free base)

δ: 7.98(s,1H), 7.12(s,1H), 4.35(t,2H), 3.35(t,2H), 3.08(brd, 2H), 2.85(t,2H), 2.5-2.3(m,2H), 2.2-1.92(m,4H), 1.9-1.2(m,9H), 0.92(t,3H)

Example 9

6-Chloro-2,2-dimethyl-[2H]-3,4-dihydro-1-benzopyran-8-(l-butyl-4-piperidyl)methyl carboxylate hydrochloride (E9)

Following the procedure outlined in Example 4,6-chloro-2,2-dimethyl-[2H]-3,4-dihydro-l-benzopyran-8-carboxylic acid (D5) (1g) was converted to the title compound (310mg)

^{1}H NMR 250 MHz ($CDCl_3$) (free base)

δ: 7.55(d,1H), 7.16(d,1H), 4.13(d,2H), 2.98(bd, 2H), 2.79(t,2H), 2.32(t,2H), 1.68-2.00(m,7H), 1.24-1.54(m,12H inc s,6H), 0.92(t,3H)

Example 10

(1-Butyl-4-piperidyl)methylthiochroman-8-carboxylate (E10)

This was prepared according to the general method described in Example 1. Thus thiochroman-8-carboxylic acid (0.160g, 0.825 mmol) (D6) was converted to the title compound (0.145g, 53%) which was subsequently transformed into its hydrochloride salt m.pt 157-158°C.

^{1}H NMR (250 MHz, $CDCl_3$) (free base),

δ: 7.82 (d, 1H), 7.17 (d, 1H), 7.00 (t, 1H), 4.15 (d, 2H), 3.00 (m, 4H), 2.87 (t, 2H), 2.38 (t, 2H), 2.20-1.95 (m, 5H), 1.80 (m, 2H), 1.50 (m, 4H), 1.30 (m, 2H), 0.90 (t, 3H).

Example 11

(1-Butyl-4-piperididyl)methyl-6-bromothiochroman-8-carboxylate (E11)

This was prepared according to the general method described in Example 1. Thus 6-bromothiochroman-8-carboxylic acid (0.318g, 1.17mmol) (D7) was converted to the title compound (0.217g, 44%) which was subsequently transformed into its hydrochloride salt. m.pt. 197-198°.

^{1}H NMR (200 MHz, $CDCl_3$) (free base)

δ: 7.90 (d, 1H), 7.30 (d, 1H), 4.20 (d, 2H), 3.00 (m, 4H), 2.88 (t, 2H), 2.32 (t, 2H), 2.10 (m, 2H), 2.00-1.70 (m, 4H), 1.55-1.20 (m, 7H), 0.92 (t, 3H).

Example 12

5-Amino-(1-butyl-4-piperidyl)methyl-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxamide (E12)

A solution of 5-amino-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid (D4, 200mg) in acetonitrile (6ml) was treated with bis-carbonyldiimidazole (171mg) and the resulting solution was stirred at room temperature for 2 hours. A solution of (1-butyl-4-piperidyl) methylamine (150mg) in acetonitrile (10ml) was added and the reaction mixture was stirred at room temperature for 15 hours. The solvent was removed *in vacuo* and the residue partitioned between water and dichloromethane. The dichloromethane layer was removed and the aqueous extracted further with dichloromethane. The organic extracts were combined and washed with water, then dried (Na_2SO_4) and concentrated to give a yellow gum that was purified by column chromatography on silica using $CHCl_3$ with increasing quantities of MeOH as eluant to give the title compound as an off white solid , 30mg mp 65-6^{o}C.

^{1}H NMR (250 MHz $CDCl_3$)

δ: 8.0 (s,1H), 7.96-7.8 (m,1H), 4.45-4.15 (m,4H,) 3.32 (t,2H), 3.02 (d,2H), 2.53 (t, 2H), 2.39 (t,2H), 2.2-1.9 (m,4H), 1.86-1.15(m,9H), 0.92 (t,3H)

Descriptions

Description 1 (intermediate for Example 2)

[2H]-3,4-Dihydro-1-benzopyran-8-carboxylic acid

Following the procedure outlined in EP-A-307172 Example 15, [2H]-3,4-dihydro-1-benzopyran (0.85g) was converted to the title compound (D1) (0.77g)

^1H NMR (200MHz)($CDCl_3$)

δ: 8.0(d,1H), 7.3(d, 1H), 7.0(t,1H), 4.45(t,2H), 2.89(t,2H), 2.25-2.0(m,2H)

Description 2 (intermediate for Example 2)

2,3-Dihydrobenzofuran-7-carboxylic acid

Following the procedure outlined in EP-A-307172, Example 15, 2,3-dihydrobenzofuran (0.59g) was converted to the title compound (D2) (0.41g)

^1H NMR 250MHz ($CDCl_3$)

δ: 7.82(d,1H), 7.44(d,1H), 6.96(t,1H), 4.80(t,2H), 3.30(t,2H)

Description 3 (intermediate for Example 3)

6-Chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid

A solution of [2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid (D1) (150mg) in glacial acetic acid (10ml) was treated with a solution of 1.3 equivalents of chlorine (80mg) in glacial acetic acid (2.8 mls) dropwise with ice-cooling. After stirring overnight at ambient temperature the solvents were evaporated under reduced pressure, and the residue triturated with diethyl ether to give the title compound (D3) (64mg, 36%).

^{1}H NMR 200 MHz ($CDCl_3$)

δ: 10.78 (brs, 1H), 7.95 (s, 1H), 7.25 (s, 1H), 4.45 (t, 2H), 2.88 (t, 2H), 2.25-2.0 (m, 2H)

Description 4 (intermediate for Example 6)

a) **Methyl(4-acetylamino-2-propargyloxy)benzoate**

A solution of methyl-4-acetylamino-2-hydroxybenzoate (prepared as described in EP-A-234872) (5 g) in a mixture of dry tetrahydrofuran (100 ml) and dry dimethylformamide (150 ml) was treated with 1 equivalent of sodium hydride (0.72g of an 80% dispersion in oil). After stirring for 1 hour under nitrogen, 2.5 equivalents of propargylbromide (5.33 ml) were added, and the mixture was heated under reflux for three days. The solvents were evaporated under reduced pressure and the residue partitioned between 10% sodium hydroxide and ethyl acetate. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure to give a red oil which, after trituration with 60^o-80^o petrol-ether gave the title compound as a light tan powder (4.95g, 84%)

^{1}H NMR 200 MHz ($CDCl_3$)

δ: 7.91(brs, 1H), 7.81(d,1H), 7.68(s,1H), 7.05(d,1H), 4.78(d,2H), 3.86(s,3H), 2.54(m,1H), 2.2(s,3H)

b) Methyl(5-acetamido-[2H]-1-benzopyran)-8-carboxylate

A solution of methyl(4-acetamido-2-propargyloxy)benzoate (6.38g) in 1,2-dichlorobenzene (65ml) was heated under reflux under nitrogen for 60 hours. The solvent was evaporated under reduced pressure and the residue purified on a silica column, eluting with methanol/chloroform, to give the title compound as a tan solid (3.47g, 54%)

^1H NMR 200 MHz ($CDCl_3$)

δ: 7.79(brs, 1H), 7.64(d,1H), 7.3(d,1H), 6.46(d,1H), 5.85(m,1H), 4.75(brs,2H), 3.85(s,3H), 2.20(s,3H)

c) Methyl(5-acetamido-[2H]-3,4-dihydro-1-benzopyran)-8-carboxylate

A solution of methyl (5-acetamido-[2H]-1-benzopyran)-8-carboxylate (D23) (770mg) in ethanol, was hydrogenated over 10% palladium on charcoal at atmospheric pressure for 1.25 hours. The reaction mixture was filtered and the filtrate evaporated under reduced pressure to give the title compound as a white powder (670 mg, 86%)

^1H NMR 250 MHz ($CDCl_3$)

δ: 7.68(d,1H), 7.49(brs, 1H), 7.19(brs,1H), 4.22(t,2H), 3.88(s,3H), 2.62(t,2H), 2.20(s,3H), 2.1-1.96(m,2H)

d) Methyl(5-acetamido-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylate

Following the procedure outlined in Description 3, methyl(5-acetamido-[2H]-3,4-dihydro-1-benzopyran)-8-carboxylate (660mg) was converted to the title compound which was isolated as a light tan powder (525mg, 70%)

^1H NMR 250 MHz ($CDCl_3$)

δ: 7.7(s,1H), 7.15(s,1H), 4.29(t,2H), 3.89(s,3H), 2.70(t,2H), 2.25(s,3H), 2.05-1.9(m,2H)

e) 5-Amino-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylic acid

A solution of methyl (5-acetamido-6-chloro-[2H]-3,4-dihydro-1-benzopyran-8-carboxylate (1.015g) in ethanol (20 ml) water (10 ml) and 10% sodium hydroxide (30 ml) was heated under reflux for 24 hours, then cooled and treated with concentrated hydrochloric acid (until pH 2) and the resulting precipitate was filtered off to give the title compound (D4) (427mg, 52%)

^{1}H NMR 250 MHz ($CDCl_3$)

δ: 7.85(s,1H), 4.34(t,2H), 2.54(t,2H), 2.25-2.0(m,2H)

Description 5 (intermediate for Example 9)

6-Chloro-2,2-dimethyl-[2H]-3,4-dihydro-l-benzopyran-8-carboxylic acid

Following the procedure outlined in Description 3, 2,2-dimethyl-[2H]-3,4-dihydro-l-benzopyran-8-carboxylic acid (EP-A-307172) (2.41g) gave the title compound (D5) (2.68g). M^+ 240 (E1)

Description 6 (intermediate for Example 10)

a) Methylthiochroman-4-one-8-carboxylate

β-(2-carbomethoxythiophenoxy) propionic acid (6.00g, 0.025mol) (I.W. Still and M.J. Thomas J.Org. Chem 1968, 2733) was added slowly to ice cooled conc. sulphuric acid (75ml) with stirring. After 21h, the reaction mixture was poured into ice water and then made alkaline using solid sodium hydrogen carbonate. The resultant suspension was then extracted with CH_2Cl_2(3X). The combined organic layers were then dried (Na_2SO_4), and evaporated under reduced pressure to give an orange oil which was dried *in vacuo* and crystallised on standing to give (2.40g, 43%).

b) Methylthiochroman-4-ol-8-carboxylate

Methylthiochroman-4-one-8-carboxylate (0.500g, 2.25mmol) was dissolved with stirring in ethanol (20 ml). After 1h, the reaction mixture was evaporated under reduced pressure and the residue partitioned between ethyl acetate and water. The aqueous layer was then extracted with ethyl acetate (1X) and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil, which was purified by silica-gel chromatography (1:1 Pentane:EtOAc as eluant) to give the title compound as a colourless oil (0.499g, 99%)

^{1}H NMR (200 MHz, $CDCl_3$) δ: 7.95 (dd, 1H), 7.55 (dd, 1H), 7.12 (t, 1H), 4.87 (m, 1H), 3.92 (s, 3H) 3.23 (m, 1H), 2.88 (m, 1H), 2.37 (m, 1H), 2.08 (m, 1H), 1.92 (d, 1H).

c) Methyl-2H-thiochromene-8-carboxylate

Methyl thiochroman-4-ol-8-carboxylate (0.337g, 1.50 mmol) was dissolved in toluene (25ml) and was treated with p-toluenesulphonic acid (0.028g, 0.15 mmol). The mixture was then heated to reflux with stirring. After 2h, the reaction mixture was allowed to cool and was washed with sodium hydrogen carbonate solution. The aqueous layer was then extracted with EtOAc (1X), and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a pale yellow oil which was purified by silica-gel chromatography (pentane: Et_2O 2:1 as eluant) to give the title compound

(D2b) as a pale yellow oil (0.270g, 87%)

^{1}H NMR (200 MHz, $CDCl_3$, δ: 7.80 (dd, 1H), 7.20 (dd, 1H), 7.10 (t, 1H), 6.52 (d, 1H), 6.02 (m, 1H), 3.92 (s, 3H), 3.48 (dd, 1H).

d) Methylthiochroman-8-carboxylate

Methyl-2H-thiochromene-8-carboxylate (1.83g, 8.88 mmol) was dissolved in ethanol (100ml) and treated with 10% PdC (1.5g). The mixture was then hydrogenated at atmospheric pressure at room temperature. After 19h the reaction mixture was filtered through celite and evaporated under reduced pressure to give a colourless oil which was dried *in vacuo* to give the title compound (1.25g, 68%)

^{1}H NMR (200 MHz, $CDCl_3$), δ 7.80 (d, 1H), 7.62 (d, 1H), 6.97 (t, 1H), 3.89 (s, 3H), 2.97 (t, 2H), 2.87 (t, 2H), 2.12 (m, 2H).

e) Thiochroman-8-carboxylic acid

Methylthiochroman-8-carboxylate (0.220g, 1.05mmol) was dissolved in ethanol (5ml) and treated with 10% sodium hydroxide solution (10ml). The mixture was then heated to reflux with stirring. After 5h, the reaction mixture was allowed to cool. The ethanol present was then removed by evaporation under reduced pressure. The aqueous residue was then washed with CH_2Cl_2 (2X) before being acidified to pH1 using 5M HCl. The resultant pale yellow precipitate was then filtered off and dried *in vacuo* to give the title compound (0.156g, 76%) (D6).

^{1}H NMR (200 MHz, CD_3OD)

δ: 7.80 (d, 1H), 7.20 (d, 1H), 7.00 (t, 1H), 2.90 (m, 4H), 2.08 (m, 2H).

Description 7 (intermediate for Example 11)

a) Methyl-6-bromothiochroman-8-carboxylate

A solution of methylthiochroman-8-carboxylate (0.300g, 1.44 mmol) (D6a) in dichloromethane (20ml) was treated with bromine (0.106 ml, 2.07 mmol) and the reaction mixture left at room temperature. After 4 days the reaction mixture was washed with sodium metabisulphile solution. The organic layer was then dried (Na_2SO_4) and evaporated under reduced pressure to give the title compound as a colourless oil (0.340g, 82%).

^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.92 (d, 1H), 7.30 (d, 1H), 3.92 (s, 3H), 3.00 (t, 2H), 2.88 (t, 2H), 2.10 (m, 2H).

b) 6-Bromothiochroman-8-carboxylic acid

This was prepared according to the general method described in Description 6e). Thus, methyl-6-bromo-thiochroman (0.325g, 1.13mmol) was converted to the title compound (0.306g, 99%) (D7).

^{1}H NMR (200MHz, CD_3SOCD_3) : 13.25 (brs, 1H), 7.82 (d, 1H), 7.50 (d, 1H), 2.92 (m, 4H), 2.00 (m, 2H).

5-HT_4 RECEPTOR ANTAGONIST ACTIVITY

1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}M and granisetron 10^{-6}M to block effects at 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 4[illegible]-70% maximum(10^{-9}M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT_4 receptor antagonist are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP. From this data, pIC_{50} values are determined, being defined as the -log concentration of antagonist which reduces the contraction by 50%. A compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor antagonist.

Compounds were generally active in the range of concentrations of the order of pIC_{50}=7 or more, E3, E8 and E12 showing particularly good activity.

2) Piglet Atria

Compounds were tested in the piglet spontaneous beating screen (Naunyn-Schmiedeberg's Arch. Pharmacol 342, 619-622). pK_B ($-\log_{10} K_B$) value for the compound of Examples 3 and 7 were 9.8 and 7.7 respectively.

3) Rat oesophagus

Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et. al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The inner smooth muscle tube of the muscularis mucosae is isolated and mounted for isometric tension recording in oxygenated (95% O_2/5% CO_2) Tyrodes solution at 37°C. All experiments are performed in pargyline pre-treated preparations (100μM for 15 min followed by washout) and in the presence of cocaine (30μM). Relaxant responses to 5-HT are obtained after pre-contracting the oesophagus tissue with carbachol (3μM).

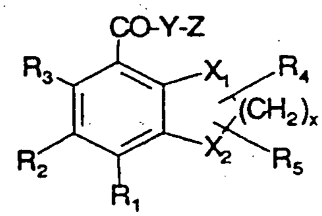
4) 5-HT-induced motility in dog gastric pouch

Compounds are tested in the *in vivo* method described in "Stimulation of canine motility by BRL 24924, a new gastric prokinetic agent", Bermudez *et al*, J. Gastrointestinal Motility, 2(4), 281-286.

The compound E3 showed inhibition at a dose of 10μg kg^{-1}.

Claims

1. A compound of formula (I), or a pharmaceutically acceptable salt thereof



(I)

in which X_1-$(CH_2)_x$-X_2 and the aromatic carbon atoms to which they are attached form a 5-7 membered ring

wherein:

one of X_1 and X_2 is O, S or CH_2 and the other is CH_2;

x is 1, 2 or 3;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

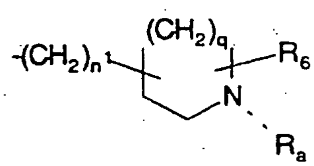
R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

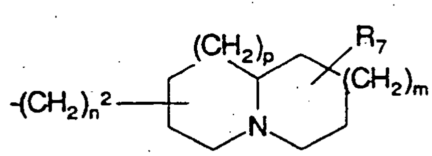
R_4 and R_5 are independently hydrogen or C_{1-6} alkyl;

Y is O or NH;

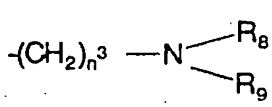
Z is of sub-formula (a), (b) or (c):



(a)



(b)



(c)

wherein
n^1 is 1, 2, 3 or 4; n^2 is 1 or 2; n^3 is 2, 3, 4 or 5;
q is 0, 1, 2 or 3; p is 0, 1 or 2; m is 0, 1 or 2;
R_a is hydrogen or a lipophilic group, such as C_{1-12} alkyl or aralkyl;or
R_a is $(CH_2)_r$-R_{10} wherein r is 2 or 3 and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, $-CR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl; and
R_6, R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and
R_9 is hydrogen or C_{1-10} alkyl;
or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere.

2. A compound according to claim 1 wherein R_1 is hydrogen or amino.

3. A compound according to claim 1 or 2 wherein R_2 is hydrogen or halo.

4. A compound according to claim 1, 2, or 3 wherein R_3 is hydrogen or halo.

5. A compound according to claim 1, 2, 3 or 4 wherein X_1-$(CH_2)_x$-X_2 is O-$(CH_2)_2$-CH_2, O-$(CH_2)_3$-CH_2, O-CH_2-CH_2, or corresponding values wherein $X_1 = X_2 = CH_2$, wherein any of the methylene linkages are optionally mono- or di-substituted by C_{1-6} alkyl groups, such as methyl.

6. A compound according to any one of claims 1 to 5 wherein Y is O or NH.

7. A compound according to any one of claims 1 to 6 wherein Z is of sub-formula (a) and $(CH_2)_n1$ is attached at a carbon atom of the azacycle.

8. A compound according to claim 7 wherein Z is N-substituted 4-piperidylmethyl.

9. A compound according to claim 8 wherein the N-substituent is C_2 or greater alkyl, or optionally substituted benzyl.

10. A compound according to claim 1 selected from the compounds E1 to E12 inclusive, as described herein, including pharmaceutically acceptable salts thereof.

11. A process for preparing the ester or amide compounds according to claim 6, which comprises reacting an appropriate benzoic acid derivative with an appropriate alcohol or amine.

12. A pharmaceutical composition comprising a compound according to any one of claims 1 to 10, and a pharmaceutically acceptable carrier.

13. A compound according to claim 1 for use as an active therapeutic substance.

14. The use of a compound according to claim 1 in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

15. The use according to claim 14 for use as a 5-HT_4 antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

INTERNATIONAL SEARCH REPORT

International Application No PCT/GB 93/00214

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D405/12; C07D409/12; A61K31/445

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
X	EP,A,0 234 872 (ADRIA LABORATORIES) 2 September 1987 cited in the application see pages 2-3; table pages 6-12, compounds 16-18,22-32,36,42,44,48,50,53,54,56-58,63, 66,67,69-75; table VI, compounds 13a,13b, 13e-13k; table VII, compounds 16a-c,16k, 16l ---	1-6,12
X	EP,A,0 231 139 (LABORATOIRES DELAGRANGE) 5 August 1987 see page 1 - page 2; examples 10,20,21 -----	1-6,12

° Special categories of cited documents : [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

1

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
15 MARCH 1993	26. 03. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	RUSSELL F. ENGLISH

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

GB 9300214
SA 69873

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 15/03/93
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82